

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

To:

see form PCT/ISA/220

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2005/001344

International filing date (day/month/year)
06.04.2005

Priority date (day/month/year)
08.04.2004

International Patent Classification (IPC) or both national classification and IPC
C07B59/00, C07C17/20, C07C17/361, C07C25/13, C07C45/63, C07C49/807, C07C49/84, C07D239/553,

Applicant
GE HEALTHCARE LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Seufert, G

Telephone No. +49 89 2399-8330



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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2-6, 8-18, 21-24, 26-27
	No: Claims	1, 7, 19, 20, 25, 28
Inventive step (IS)	Yes: Claims	5, 6
	No: Claims	1-4, 7-28
Industrial applicability (IA)	Yes: Claims	1-28
	No: Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

- D1 BULL. ACAD. SCI. USSR DIV. CHEM. SCI. (ENGL. TRANSL.), vol. 10, 1984, pages 2130-2135
- D2 WO 03/002157 A
- D3 JOURNAL OF FLUORINE CHEMISTRY, vol. 21, 1982, pages 385-392
- D4 J. LABEL. COMPD. RADIOPHARM., vol. 46, 2003, pages 699-713
- D5 JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, vol. 13, 1998, pages 2043-2046

V. Reasoned statement with regard to novelty, inventive step or industrial applicability

Novelty

The present application refers to a method for the production of an aromatic or heteroaromatic fluorine-labelled compound comprising fluoridation of an iodonium salt with a fluoride ion source characterised in that the reaction solvent comprises water (claim 1) and to a kit for the production of an aromatic fluorine labelled compound comprising a vial containing an aqueous solvent and a reaction vessel containing an iodonium salt.

Document D1 describes the reaction of a diphenyliodonium tetrafluoroborate with NaF in the following systems: $\text{CHCl}_3\text{-H}_2\text{O}$ and $\text{C}_2\text{H}_4\text{Cl}_2\text{-H}_2\text{O}$. The subject-matter of claim 1 as well as claim 7 is therefore not considered to meet the requirement of Art. 33(2) PCT.

Although not explicitly disclosed in D1, a novel teaching for a kit according to claim 19 is not apparent. It is furthermore, not apparent in what way claims 19, 20, 25 and 28 are distinguished from D4 (or D5). The fluoride ion is present in water before the resolubilisation and the iodonium ion falls under the general formula (I) of claim 8. It should be noted that the way a product (kit) is used is not considered to be a suitable distinguishing feature for a product (kit). Thus, claims 19, 20, 25 and 28 are also not considered to meet the requirement of Art. 33(2) PCT.

The features of the dependent claims 2-6, 8-18 and 21-24, 26-27 are not explicitly disclosed in combination with the features of claims 1 or 19. These claims therefore appear to meet the requirement of Art. 33(2) PCT.

Inventive step

The subject-matter of claim 1, as far as it is novel, is not considered to be inventive in view of the teaching of D1. D1 shows that fluoridation with a fluoride ion is possible in a reaction solvent comprising water, although the reaction might be slow. With regard to the preparation of [^{18}F]-labelled compounds, it seems also doubtful that the technical problem of efficiently providing radiofluoridated compounds is solved in aqueous systems as disclosed in D1 due to the slow reaction and the relatively short half life of [^{18}F]. These aqueous systems are, however, included in the present claim 1. Furthermore, the use of a solid-phase in the nucleophilic fluorination is known in the art, see D2. Claim 1 as well as the dependent claims 8-18 are therefore not considered to meet the requirement of Art. 33(3) PCT.

Furthermore, to be considered inventive the technical problem should be solved basically over the whole scope of the claims. The claims include the possibility of water being the only solvent or the major part of the solvent mixture. This, however, is not supported by the application. None of the examples is carried out in water or in water being the major part of the solvent mixture. Furthermore, the examples apparently suggest that too high an amount of water should not be present in order to efficiently produce the fluoridated compounds (see application table II). Claims 2-4 are therefore not considered to meet the requirement of Art. 33(3) PCT.

The subject-matter of the dependent claims 5 and 6 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

The fluoridation of an iodonium salt with a fluoride source in water-miscible solvents, like acetonitrile, is typically carried out in the absence of water, see D2-D5 and the application page 1, line 14 - page 3, line 2. Even D1, which refers to the use of

systems of water-immiscible solvents and water, teaches that the absence of water improves the reaction.

The application has demonstrated that, contrary to the teaching of the prior art, the presence of a certain amount of water in a water-miscible solvent actually improves the reaction (see application, tables II, III and IV). This was not obvious for the skilled person from any of the available documents. The subject-matter of claims 5 and 6 appears therefore to meet the requirement of Art. 33(3) PCT.

Even in case novelty has to be acknowledged for the subject-matter of claim 19, no inventive step can be seen in the subject-matter of this claim. The inventive concept of the present application can be seen in the fluoridation of an iodonium salt using of a solvent mixture of a certain amount of water and a water-miscible solvent, i.e. a process feature. This concept is not reflected in claim 19, because a kit is not limited to a particular way of using it, i.e. it is not excluded that water is eliminated from the fluoride source before its use, as it is done in D4 or D5.

Claim 19 as well as the dependent claims 20-28 are not considered as involving an inventive step contrary to the requirement of Art. 33(3) PCT.

Industrial applicability

There are no objections against the industrial applicability of the presently claimed subject-matter.

Further remarks:

It seems to be clear from the description on page 5, line 30 - page 6, line 5 and page 7, lines 5-6 that it is essential that the aromatic or heteroaromatic ring system is electron deficient. Since independent claim 1 does not contain this feature it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of

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the invention.

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.